# PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH
UNITED KINGDOM

RECEIVED
12 NOV 2004
GILL JENNINGS & EVERY

## NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 12/11/2004 |
| Applicant's or agent's file reference HMJ03637WO | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| International application No. PCT/GB2004/003511 | International filing date *(day/month/year)* 12/08/2004 |
| Applicant LIPOXEN TECHNOLOGIES LIMITED | |

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   **Filing of amendments and statement under Article 19:**
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   **When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   **Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   **For more detailed instructions,** see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

| Name and mailing address of the International Searching Authority | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Laura Fernández Gómez |

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | FOR FURTHER ACTION | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
|---|---|---|
| HMJ03637WO | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/GB2004/003511 | 12/08/2004 | 12/08/2003 |
| Applicant | | |
| LIPOXEN TECHNOLOGIES LIMITED | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [X] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/003511

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08B37/00 C07K17/12 A61K39/385 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br><br><br>A | EP 0 454 898 A (SEIKAGAKU KOGYO CO LTD)<br>6 November 1991 (1991-11-06)<br>cited in the application<br>claims 7,9<br><br>page 5, lines 22-46 | 1,2,5-7,<br>10-19,<br>21-31<br>3,4,8,9,<br>20 |
| X<br><br><br>A | US 4 356 170 A (JENNINGS HAROLD J ET AL)<br>26 October 1982 (1982-10-26)<br>cited in the application<br>claims 1,2,4,6-8,16<br><br>column 3, lines 8-39<br>column 4, lines 27-44 | 1,2,5-7,<br>10-19,<br>21-31<br>3,4,8,9,<br>20 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 5 November 2004 | 12/11/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Gerber, M |

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5 097 020 A (ANDERSON PORTER W ET AL) 17 March 1992 (1992-03-17) | 1,2,5-7, 10-19, 21-31 |
| A | column 4, lines 22-62<br>column 2, line 7<br>column 3, lines 63-65 | 3,4,8,9, 20 |
| X | SEN G ET AL: "The specificity of the binding site of AchatininH, a sialic acid-binding lectin from Achatina fulica" 1 March 1995 (1995-03-01), CARBOHYDRATE RESEARCH, ELSEVIER SCIENTIFIC PUBLISHING COMPANY. AMSTERDAM, NL, PAGE(S) 115-125 , XP004022107<br>ISSN: 0008-6215 | 32-34, 36-45 |
| A | *O-deacetylation of BSM on page 117*<br>*Periodate oxidation of glycoproteins on page 117* | 35 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-31

Claims 1-18
Process for producing an aldehyde derivative of a sialic acid compound in which a starting material having a sialic acid at the reducing terminal unit is subjected to:
a)- reduction to form a vicinal diol group,
b)- selective oxidation to oxidise the vicinal diol group formed in step a) to form an aldehyde group.
Claims 19-29
Aldehyde derivative of a di-, oligo- or polysaccharide comprising at least one sialic acid unit.
Claims 30
Composition comprising a compound according to claim 19-29 and a diluent.

Claim 31
Pharmaceutical composition comprising a compound according to claims 25 or 28 and a pharmaceutically acceptable excipient.

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2. claims: 32-45

Claims 32-37
Process in which a sialic acid starting material having a terminal sialic acid unit at a non-reducing terminal end is subjected to:
c)- selective oxidation to form an aldehyde group,
d)- reduction to reduce the aldehyde to the corresponding alcohol.
Claims 38-43
Compound of formula II being a derivative of mono-, di-, oligo- or polysaccharide.
Claim 44
Pharmaceutical composition comprising a compound according to claim 43 and a pharmaceutically acceptable excipient.
Claim 45
Composition comprising a compound according to claims 38-43 and a diluent.

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/003511

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB2004/003511

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0454898 A | 06-11-1991 | JP 2975632 B2 | 10-11-1999 |
| | | JP 3284698 A | 16-12-1991 |
| | | AT 135375 T | 15-03-1996 |
| | | AU 649416 B2 | 26-05-1994 |
| | | AU 6450690 A | 31-10-1991 |
| | | CA 2027447 A1 | 01-10-1991 |
| | | DE 69025920 D1 | 18-04-1996 |
| | | DE 69025920 T2 | 14-08-1996 |
| | | DK 454898 T3 | 15-04-1996 |
| | | EP 0454898 A1 | 06-11-1991 |
| | | ES 2083989 T3 | 01-05-1996 |
| | | FI 905003 A | 01-10-1991 |
| | | KR 188382 B1 | 01-06-1999 |
| | | NO 904378 A ,B, | 01-10-1991 |
| | | US 5310881 A | 10-05-1994 |
| US 4356170 A | 26-10-1982 | CA 1181344 A1 | 22-01-1985 |
| US 5097020 A | 17-03-1992 | US 4673574 A | 16-06-1987 |
| | | US 4902506 A | 20-02-1990 |
| | | US 5360897 A | 01-11-1994 |
| | | MX 9203151 A1 | 01-07-1992 |
| | | US 4762713 A | 09-08-1988 |
| | | US 4761283 A | 02-08-1988 |
| | | AT 96676 T | 15-11-1993 |
| | | AU 601742 B2 | 20-09-1990 |
| | | AU 7393587 A | 01-12-1987 |
| | | CA 1276109 C | 13-11-1990 |
| | | DE 3787995 D1 | 09-12-1993 |
| | | DE 3787995 T2 | 19-05-1994 |
| | | DE 10199036 I1 | 10-01-2002 |
| | | DE 10199037 I1 | 22-11-2001 |
| | | DK 2588 A | 05-01-1988 |
| | | EP 0245045 A2 | 11-11-1987 |
| | | ES 2059372 T3 | 16-11-1994 |
| | | HK 1003326 A1 | 23-10-1998 |
| | | IE 60897 B1 | 24-08-1994 |
| | | JP 2736248 B2 | 02-04-1998 |
| | | JP 8283282 A | 29-10-1996 |
| | | JP 2559438 B2 | 04-12-1996 |
| | | JP 1500036 T | 12-01-1989 |
| | | LU 90808 A9 | 25-09-2001 |
| | | LU 90809 A9 | 25-09-2001 |
| | | NL 300051 I1 | 01-10-2001 |
| | | NL 300052 I1 | 01-10-2001 |
| | | WO 8706838 A1 | 19-11-1987 |

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/GB2004/003511 | 12.08.2004 | 12.08.2003 |

International Patent Classification (IPC) or both national classification and IPC
C08B37/00, C07K17/12, A61K39/385, A61K47/48

Applicant
LIPOXEN TECHNOLOGIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Gerber, M

Telephone No. +49 89 2399-8528

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/003511



**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/003511

**Box No. II Priority**

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**Box No. IV Lack of unity of invention**

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 3, 4, 8, 9, 20, 35 |
| | No: | Claims | 1, 2, 5-7, 10-19, 21-34, 36-45 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-45 |
| Industrial applicability (IA) | Yes: | Claims | 1-45 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Re Item IV**

This Authority considers that there are two inventions covered by the claims indicated as follows:

I: *Claims 1-31* directed to a process for **producing an aldehyde derivative of a sialic acid compound** in which a starting material having a **sialic acid unit at the reducing terminal unit** is subjected to:

a)- reduction to form a vicinal diol group,

b)- selective oxidation to oxidise the vicinal diol group formed in step a) to form an aldehyde group.

and an **aldehyde derivative of a di-, oligo- or polysaccharide comprising at least one sialic acid unit**, a composition comprising such a compound and a diluent, and a pharmaceutical composition comprising a compound according to claims 25 or 28 and a pharmaceutically acceptable excipient.

The feature common to the claims 1-31 is the aldehyde derivative of claim 18.

II: *Claims 32-45* directed to a process in which a sialic acid starting material having a terminal **sialic acid unit at a non-reducing terminal end** is subjected to:

c)- selective oxidation to form an aldehyde group,

d)- reduction to reduce the aldehyde to the corresponding **alcohol**.

and a compound of formula II, being a derivative of mono-, di-, oligo- or polysaccharide, a pharmaceutical composition comprising a compound according to claim 43 and a pharmaceutically acceptable excipient, and a composition comprising a compound according to any of claims 38-43 and a diluent.

The feature common to the claims 32-45 is the compound of formula II of claim 38.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows.

The prior art has been identified as document EP-A-0 454 898 and discloses a glycosaminoglycan-modified protein wherein an amino group of a protein is bound to an aldehyde group, which has been formed by reducing and partially oxidising the reducing terminal sugar moiety of a glycosaminoglycan such as colominic acid.

It follows that there is no common contribution over the prior art.

Also, examining the possible correspondence by technical effect, one finds that the technical effect of:

- the first invention is the **activation of the reducing end** of the sialic acid starting material to allow reaction with a protein,
- the second invention is the **desactivation of the non-reducing end** of the sialic acid starting material to avoid reaction with a protein.

This appears to show lack of corresponding technical effect as well. Consequently, neither the objective problem underlying the subjects of the claimed inventions, nor their solutions defined by the special technical features allow for a relationship to be established between the said inventions, which involves a single general inventive concept.

In conclusion, the groups of claims are not linked by common or corresponding special technical features and define two different inventions not linked by a single general inventive concept.

The application, hence, does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

**D1:** EP-A-0 454 898 (SEIKAGAKU KOGYO CO LTD) 6 November 1991

**D2:** US-A-4 356 170 (JENNINGS HAROLD J ET AL) 26 October 1982

**D3:** US-A-5 097 020 (ANDERSON PORTER W ET AL) 17 March 1992

**D4:** GOUTAM SEN, CHITRA MANDAL: "The specificity of the binding site of Achatinin$_H$, a sialic acid-binding lectin from Achatina fulica" CARBOHYDRATE RESEARCH, vol. 268, 1995, pages 115-125, XP002303034

**1. Novelty**

**1.1.** The subject-matter of **claims 1, 2, 5-7, 10-19 and 21-31** is not novel over D1, D2

and D3 (Article 33(2) PCT).

D1 is directed to glycosaminoglycan-modified proteins wherein the amino group of the protein is bound to an aldehyde group formed by:

- reducing and thereby cleaving the reducing terminal sugar moiety of the glycosaminoglycan which can be colominic acid with an alkali boron hydride such as sodium boron hydride and sodium boron cyanohydride,
- followed by partially oxidising the reducing terminal sugar moiety using alkali periodates such as sodium periodate or potassium periodate (see page 5, lines 22-39, and claim 7).

The aldehyde compound is then reacted with an amino group of a protein by reductive amination (see page 5, lines 40-46). Pharmaceutical compositions containing said glycosaminoglycan-modified proteins together with a pharmaceutically acceptable carrier or diluent are also described (claim 9).

In D2, the reducing end group of an antigenic polysaccharide is made into the most susceptible site for oxidation by initially reducing it to its open chain hydroxyl form, the terminal non-reducing sialic residues containing vicinal hydroxyl groups being then oxidated to yield a reactive aldehyde group which is then covalently linked to a free amino group of a selected protein by reductive amination (see column 3, lines 8-39, column 4, lines 27-44, and claims 1, 2, 4, 6-8 and 16). The antigenic polysaccharide can be derived from Meningococci and E. coli, Meningococcal group B polysaccharide being disclosed in example 1.

D3 relates to the formation of reducing groups on the capsular polysaccharide like Neisseria meningitidis serogroup C (see column 2, line 7) by selective hydrolysis, e.g. by acids, bases or enzymes, combined with a specific oxidative cleavage, e.g. by periodate or related oxygen acids (see column 3, lines 63-65) to form aldehyde groups via which the capsular polysaccharide can be covalently attached to bacterial toxins or toxoids by means of reductive amination (see column 4, lines 22-62).

**1.2.** D4 anticipates the subject-matter of **claims 32-34 and 36-45** (Article 33(2) PCT).

D4 teaches that the oxidation of the trihydroxypropyl side chain of the sialic acid residue at the non-reducing end of the sialic acid-containing chain such as colominic acid, with periodate followed by borohydride treatment, i.e. reduction of the C-7 aldehyde group to a primary alcohol abolishes the inhibitory potency of said sialic acid compound towards

the sialic acid binding lectin $ATN_H$.

**1.3.** The subject-matter of **claims 3, 4, 8, 9, 20 and 35** is novel over the cited prior art (Article 33(2) PCT).

It seems that the crux of the present invention is to provide better defined products of protein-conjugation-with-PSAs,-the-polysialic-acid-being-monofunctional-i.e. activated at the reducing end with an aldehyde group and passivated at the non-reducing end, thus avoiding unintended by-products during conjugation by giving rise to single-orientation attachment to proteins and avoiding the need to purify away to obtain pharmaceutically-acceptable conjugates.

It follows that the steps of:

- selective oxidation at the non-reducing end of the PSA,
- reduction at both the reducing end and the modified non-reducing end,
- selective oxidation at the modified reducing end,

are essential to the obtention of a compound which can be easily fractionated by ion exchange chromatography.

The Applicant should consider modifying its set of claims in order to better reflect the sought effect and thus also overcome the objection of lack of unity.

## 2. Inventive step

D1 is regarded as being the closest prior art to the subject-matter of claim 3.

The subject-matter of claim 3 differs from this known process in that an additional step of oxidising the vicinal diol group at the non-reducing end of the sialic acid-containing chain is performed prior to steps a) and b).

The technical problem to be solved by the present invention may therefore be regarded as to provide a process for the provision of a monofunctional polysialic acid which can be fractionated by ion exchange chromatography.

The skilled person, face with this technical problem, would have been prompted to combine the teaching of D1 and D4 to produce a monofunctional polysialic acid activated at the reducing end with an aldehyde group and passivated at the non-

reducing end without the exercise of inventive skill (Article 33(3) PCT).

The features of dependent **claims 4, 8, 9** are known. It would therefore be obvious to the person skilled in the art, to apply these features.

The compound of **claim 20** and the process of **claim 35** are obvious too.

## 3. Industrial applicability

The subject-matter of present **claims 1-45** appears to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.